

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/154659>

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

CORRESPONDENCE



Blood Pressure in Early Autosomal Dominant Polycystic Kidney Disease

TO THE EDITOR: In the Halt Progression of Polycystic Kidney Disease (HALT-PKD) study, Schrier et al. (Dec. 11 issue)¹ randomly assigned patients with early-stage autosomal dominant polycystic kidney disease (ADPKD) to either a standard blood-pressure target or a low blood-pressure target. The low blood-pressure target was associated with a slower increase in total kidney volume, but not with an overall change in the estimated glomerular filtration rate (GFR). The latter finding might be viewed as being disappointing. However, we would caution that the institution of strict blood-pressure control will result in an acute, hemodynamic, but reversible decrease in the estimated GFR.

A recent scientific workshop sponsored by the U.S. National Kidney Foundation and the Food and Drug Administration concluded that this acute effect is not indicative of irreversible loss of nephrons.² Accordingly, rather than using the baseline estimated GFR, we would suggest comparing only on-treatment slopes of the estimated GFR. Such an analysis does show a benefit associated with the low blood-pressure target ($P=0.05$).¹ Since a decrease in the estimated GFR is a late phenomenon in many patients with ADPKD,³ a subgroup analysis of on-treatment estimated GFR slopes with the use of forest plots would be of interest, since it might hint at whether certain subgroups of patients with early-stage disease might benefit from a low blood-pressure target.

A. Lianne Messchendorp, M.D.
Ron T. Gansevoort, M.D., Ph.D.

University Medical Center Groningen
Groningen, the Netherlands
r.t.gansevoort@umcg.nl

No potential conflict of interest relevant to this letter was reported.

1. Schrier RW, Abebe KZ, Perrone RD, et al. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med* 2014;371:2255-66.
2. Levey AS, Inker LA, Matsushita K, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis* 2014;64:821-35.
3. Grantham JJ, Chapman AB, Torres VE. Volume progression in autosomal dominant polycystic kidney disease: the major factor determining clinical outcomes. *Clin J Am Soc Nephrol* 2006;1:148-57.

DOI: 10.1056/NEJMc1500332

TO THE EDITOR: Schrier and colleagues evaluated aggressive blood-pressure control with the use of dual blockade of the renin-angiotensin system in patients with ADPKD. The study also has relevance for physicians who initiated the use of such dual blockade in patients after it was reported that such treatment was more effective than single blockade of the renin-angiotensin-aldosterone system in reducing proteinuria.¹

Subsequent studies such as the Ongoing

THIS WEEK'S LETTERS

- 975 **Blood Pressure in Early Autosomal Dominant Polycystic Kidney Disease**
- 977 **Atenolol versus Losartan in Marfan's Syndrome**
- 981 **A Man with Sore Throat, Hoarseness, Fatigue, and Dyspnea**
- 982 **Infection with a Chlorophyllic Eukaryote after a Traumatic Freshwater Injury**

Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) showed that dual blockade was not effective in reducing mortality or morbidity from cardiovascular disease but rather was associated with more severe adverse events such as hyperkalemia, hypotension, and acute kidney injury.^{2,3} A recent meta-analysis therefore concluded that dual therapy should not be used.⁴

However, those studies included patients with a high preexisting risk of vascular events and death because of diabetes, cardiovascular disease, heart failure, or old age. In contrast, the study by Schrier et al. clearly showed that in a relatively young population (15 to 49 years of age) without vascular disease, dual blockade was used relatively safely and that lowering blood pressure to values of 110/75 mm Hg did not result in adverse effects. Thus, physicians who have successfully used dual blockade to reduce proteinuria in their patients may consider the continued use of such therapy in these patients.

Jack F. Wetzels, M.D., Ph.D.

Radboud University Medical Center
Nijmegen, the Netherlands
jack.wetzels@radboudumc.nl

No potential conflict of interest relevant to this letter was reported.

1. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008;148:30-48.
2. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008;372:547-53.
3. Parving H-H, Brenner BM, McMurray JJV, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;367:2204-13.
4. Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. *BMJ* 2013;346:f360.

DOI: 10.1056/NEJMc1500332

TO THE EDITOR: The HALT-PKD trial showed that in the low-blood-pressure group, as compared with the standard-blood-pressure group, the annual increase in total kidney volume was significantly less (5.6% vs. 6.6% increase per year). However, there was no benefit with regard to preservation of renal function. Blood-pressure goals were ambitious (95/60 to 110/75 mm Hg

in the low-blood-pressure-group and 120/70 to 130/80 mm Hg in the standard-blood-pressure group)¹ in these young patients with ADPKD (mean age, 36.6 to 48.7 years). Current treatment guidelines of the European and U.S. Eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure do not support the use of such low blood-pressure targets in patients with nonproteinuric or even proteinuric chronic kidney disease, but instead they suggest blood-pressure targets lower than 140/90 mm Hg in all patients. The European Society of Cardiology guidelines support blood-pressure targets lower than 130 mm Hg in patients with chronic kidney disease and overt proteinuria.^{2,3} Blood-pressure goals that are as low as those defined by the HALT-PKD trial investigators may be dangerous in elderly patients with chronic kidney disease, presumably because of the high burden of prevalent cardiovascular disease in these patients. Similarly, in a very large cohort study involving 651,749 U.S. veterans with chronic kidney disease,⁴ the optimal blood-pressure range was reported to be 130 to 149 mm Hg systolic pressure and 70 to 89 mm Hg diastolic pressure, and mortality increased markedly with blood-pressure levels lower than 120/80 mm Hg.

Urs Benck, M.D.

Bernd Krüger, M.D.

Wilhelm H. Schmitt, M.D.

University Medical Center Mannheim
Mannheim, Germany
urs.benck@umm.de

No potential conflict of interest relevant to this letter was reported.

1. Torres VE, Abebe KZ, Chapman AB, et al. Angiotensin blockade in late autosomal dominant polycystic kidney disease. *N Engl J Med* 2014;371:2267-76.
2. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension. *Eur Heart J* 2013;34:2159-219.
3. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311:507-20. [Erratum, *JAMA* 2014;311:1809.]
4. Kovesdy CP, Bleyer AJ, Molnar MZ, et al. Blood pressure and mortality in U.S. veterans with chronic kidney disease: a cohort study. *Ann Intern Med* 2013;159:233-42.

DOI: 10.1056/NEJMc1500332

THE AUTHOR REPLIES: Messchendorp and Gansevoort raise the issue of using only on-treatment

estimated GFR slopes to evaluate the benefit of therapy. In our study, patients in the low-blood-pressure group, as compared with patients in the standard-blood-pressure group, had a slower increase in total kidney volume ($P=0.006$), a greater reduction in the left-ventricular-mass index ($P<0.001$), and reduced urinary albumin excretion ($P<0.001$). We also agree that the on-treatment slope of the estimated GFR shows a benefit for the low blood-pressure group ($P=0.05$).

In patients with chronic kidney disease such as ADPKD, the degree of proteinuria is a risk factor for cardiovascular complications and a decrease in kidney function. Thus, Wetzels's point is valid in that dual renin-angiotensin blockade may be indicated if it is shown to lower urinary protein excretion significantly more than monotherapy and is safe. Such may be the case in younger patients with ADPKD.

We agree with Benck et al. that aiming for blood pressure of less than 120/80 mm Hg may not be advisable in patients with chronic kidney disease, particularly in elderly patients. However, among patients with chronic kidney disease who have type 2 diabetes, those with blood pressure lower than 130/80 mm Hg have fewer complications and longer survival than those with blood pressure lower than 140/90 mm Hg.¹

Robert W. Schrier, M.D.

University of Colorado School of Medicine
Aurora, CO
robert.schrier@ucdenver.edu

Since publication of his article, the author reports no further potential conflict of interest.

1. Schrier RW, Savage S. Appropriate Blood Pressure Control in type II diabetes (ABCD Trial): implications for complications. *Am J Kidney Dis* 1992;20:653-7.

DOI: 10.1056/NEJMc1500332

Atenolol versus Losartan in Marfan's Syndrome

TO THE EDITOR: Lacro et al. (Nov. 27 issue)¹ report no benefit of losartan, an angiotensin-receptor blocker (ARB), over the beta-blocker atenolol in respect to the rate of aortic-root dilatation in Marfan's syndrome. A possible interpretation of this study might be that ARBs are as effective as beta-blockers in the treatment of patients with Marfan's syndrome.² However, such an interpretation assumes that beta-blockers are an effective treatment option.

Beta-blockers are presently considered to be first-line therapy in patients with Marfan's syndrome. However, their benefit is debatable and not supported by robust evidence. Several observational studies and only one clinical trial³ have evaluated the effectiveness of beta-blockers in patients with Marfan's syndrome, and the results have been conflicting. Two meta-analyses also reached opposing conclusions^{4,5} (Table 1). Remarkably, no study showed a benefit of beta-blockers in preventing clinical end points (e.g., death or dissection).

As a reflection of these uncertainties, the 2010 guidelines of the American College of Cardiology Foundation and the American Heart Association recommend the use of beta-blockers, whereas the 2014 guidelines of the European

Society of Cardiology do not. If beta-blockers are not truly effective, then the study by Lacro et al. has really shown that ARBs are as effective as a placebo.

Bulat A. Ziganshin, M.D.

Sandip K. Mukherjee, M.D.

John A. Elefteriades, M.D.

Aortic Institute at Yale–New Haven Hospital
New Haven, CT
john.elefteriades@yale.edu

No potential conflict of interest relevant to this letter was reported.

1. Lacro RV, Dietz HC, Sleeper LA, et al. Atenolol versus losartan in children and young adults with Marfan's syndrome. *N Engl J Med* 2014;371:2061-71.

2. Bowen JM, Connolly HM. Of Marfan's syndrome, mice, and medications. *N Engl J Med* 2014;371:2127-8.

3. Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med* 1994;330:1335-41.

4. Gersony DR, McClaughlin MA, Jin Z, Gersony WM. The effect of beta-blocker therapy on clinical outcome in patients with Marfan's syndrome: a meta-analysis. *Int J Cardiol* 2007;114:303-8.

5. Gao L, Mao Q, Wen D, Zhang L, Zhou X, Hui R. The effect of beta-blocker therapy on progressive aortic dilatation in children and adolescents with Marfan's syndrome: a meta-analysis. *Acta Paediatr* 2011;100(9):e101-e105.

DOI: 10.1056/NEJMc1500128